



PURGED

March 2, 1998

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Refer to MIN 98-16

Mr. John Vakoutis
President
Curative Health Services, Inc.
14 Research Way
East Setauket, NY 11733

Dear Mr. Vakoutis:

During an inspection of Curative Health Services, Inc. and the HealthEast Wound Care Center, 559 Capital Boulevard, St. Paul, Minnesota, on December 2-4, 17, 18, 1997, our investigators documented serious violations of the Public Health Service Act (PHS Act) and the Federal Food, Drug, and Cosmetic Act (FD&C Act) related to the manufacture and distribution of Thrombin Induced Platelet Releasate Autologous (TIPR)(Procoren®), a human platelet derived product prepared for use in the treatment of patients with nonhealing wounds.

TIPR is a biological product subject to Section 351(a) of the PHS Act in that it is applicable to the prevention, treatment, or cure of diseases or injuries of man. TIPR is a drug within the meaning of Section 201(g) of the FD&C Act in that it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man. Section 505(a) of the FD&C Act is being violated through introduction into interstate commerce of a new drug, TIPR, with no approved new drug application (NDA) in effect, pursuant to Section 505(i) of the FD&C Act. Section 351(a) of the PHS Act is being violated in that an unlicensed biological product is sent, carried, or brought for sale, barter, or exchange in interstate commerce, because TIPR is not the subject of an approved product license application (PLA), biologics license application (BLA), or investigational new drug application (IND). At least ~~one~~ lots of TIPR have been carried by patients from Minnesota to Wisconsin between October 1995 and December 1997.

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Under Title 21, Code of Federal Regulations, (21 CFR) Part 310.4(a), a drug licensed under the PHS Act is not deemed subject to Section 505 of the FD&C Act. Therefore, if TIPR were to become the subject of an approved PLA or BLA, the product would at that time not have to be the subject of an approved NDA.

TIPR is also misbranded under Section 502(a) and 502(f)(1) FD&C Act because the promotional labeling for TIPR is false and misleading in that it contains claims that are not supported by data from adequate and well-controlled clinical trials and because the labeling fails to bear adequate directions for use.

Your product, TIPR, is a biologic drug within the meaning of Section 201(g) of the Act and subject to all drug manufacturing regulations. Our investigators documented significant violations of the Current Good Manufacturing Practices (GMPs) for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Part 211 (21 CFR 211) in that:

1. There are no stability protocols written or documentation demonstrating that accelerated and ongoing stability studies are currently conducted to support the expiration dating and storage conditions of TIPR and frozen platelet releasate (REL) [21 CFR 211.166(a)].
2. The manufacturer's expiration date of ~~XXXXXX~~ "STERILE suspension buffer" is extended with no stability data to justify the extension [21 CFR 211.137(a)].
3. Growth promotion tests are not performed on prepared media lots at the time of use for microbial limits testing of TIPR. No positive controls are used for TIPR finished product testing to assure media supports growth of microorganisms [21 CFR 211.113(a)].

The above indication of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practice Regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs so they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly

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correct these deviations may result in regulatory action without further notice. Possible actions include seizure and or injunction. This is official notification that FDA expects all your locations to be in compliance.

We acknowledge receipt of your firm's January 13, 1998, response, signed by Howard Jones, Ph.D., Senior Vice President for Technical Services, to the items cited on the form FDA-483 issued to Mindy A. Smith on December 18, 1997. Please see the attached acknowledgment for comments.

You should notify this office in writing, within 15 working days of receipt of this letter, of specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to Compliance Officer Carrie A. Hoffman at the address on the letterhead.

Sincerely,

A handwritten signature in cursive script, reading "James A. Rahto".

James A. Rahto
Director
Minneapolis District

enclosure (1)